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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,274	10/09/2007	**Rehab Al-Jamal**	MUR-06-1101	9435

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IP GROUP OF DLA PIPER LLP (US)
ONE LIBERTY PLACE
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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
07/28/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pto.phil@dlapiper.com

Office Action Summary	Application No.	Applicant(s)	
	10/576,274	AL-JAMAL ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,4-13 and 15-27* is/are pending in the application.

4a) Of the above claim(s) *5-13,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 15-16 and 19-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 6/3/08, is acknowledged.

2. Claims 1, 4-13 and 15-27 are pending.

3. Claims 5-13 and 17-18 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1, 4, 15-16 and 19-27 are under consideration in the instant application.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence.

The specification discloses the following sequences (TAEKLK) that fail to comply with the sequence rule. Applicant is reminded of the sequence rules which require a submission for all sequences of 10 or more nucleotides or 4 or more amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules. Correction is required.

5. Claim 24 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The functional modulation of beta 1 integrin "may further include an increase in TIMP1" does not further limit the claim 1 when TIMP1 is not increased.

6. The print-out of the Chemicon International website, dated Sept. 23, 2002, the datasheet petaining to the JB1a clone and the supply catalogue of Chemicon dated 2004, page 198, filed 6/3/09, are sufficient to overcome the previous rejections of the instant claims based upon the deposit of biological materials under 35 U.S.C. § 112, first paragraph.

7. In view of the amendment filed on 6/3/09, only the following rejections are remained.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4, 15-16 and newly added claims 19-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. for the same reasons set forth in the previous Office Action mailed 12/3/08.

Applicant is in possession of a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a.

Applicant's arguments, filed 6/3/09, have been fully considered, but have not been found convincing.

Applicant points to the specification at page 48, lines 15 to 22, in summarizing the findings; of: experimentation conducted by the Applicants, using a modulator or beta 1 integrin, which results in a reduction of cell death (apoptosis), suggest a common mode of action which can be applicable to a wide variety of disease conditions where the extracellular matrix is degraded and cannot be replenished. In particular, the description teaches "The potential of these findings lie in tissue repair in disease where the matrix is degraded and cannot replenished as in diseases that include but not exclusive to COPD. The finding may offer a venue for therapeutic intervention in diseases where the only current lines for therapy focus on alleviating the symptoms by the use of anti-inflammatory agents but has no potential for regaining function, This could be achieved via the administration of humanized, chimeric or human antibodies or synthetic peptides or chemicals capable of binding beta l integrin and inhibiting cell death". The specification continues "In summary, the results herein address a different potential therapeutic modality which focuses on increasing cell viability and ECM anabolism instead of decreasing catabolism". Applicants concluded that they have described a novel approach, which although exemplified in relation to the treatment of emphysema in the lung (one aspect of COPD), the Applicants identified the effects mediated by the beta 1 integrin modulator compound, in particular, inhibition of apoptosis and promotion of ECM (extracellular matrix) anabolism, result is a novel approach to the treatment of conditions not soely limited to emphysema, but also extending to othe conditions where the extracellular matrix is degraded. Centeral to the ability to apply the approach identified by the applicants of using modulation of beta 1 integrin as identified by the Applicants for the promotion of tissue repair, is the fact that beta 1 integrin modulation of the type described in this application, is shown to increase cell viability and extracellular matrix anabolism, rather than decreasing catabolism. That is the modulation of beta 1 integrin actively enhances extracellular matrix anabolism rather than merely slowing down its breakdown.

However, an adequate written description of a chemical invention requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). See MPEP 2163.

While a screening method is provided in the instant applicant for identification of compounds which modulate β1 integrin function, no compounds which act as β1 function modulator have been identified and no tissue repair treatment demonstrated. While discoveries may allow the development of screening assays to identify potential drug candidates, the actual products, the test compounds themselves, have not yet been developed. The instant claims are designed to cover these compounds or the use of them, prior to identification of the substances themselves.

There is no described or art-recognized correlation or relationship between the structure of the invention, the compound and it's β1 integrin modulation function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of compounds which inhibit apoptotic pathway, alter the MMP balance, or increase in anabolism of the extracellular matrix, which retain the features essential to the instant invention.

10. Claims 1, 4, 15-16 and newly added claims 19-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a, does not reasonably provide enablement for a method of promoting any "tissue repair" comprising the step of administering any "compound which modulates the function of beta 1 integrin" to a tissue in need of repair in claim 1, wherein the "compound modulates the metalloproteinase (MMP) balance" in claim 2, or "the compound modulated apoptosis" in claim 3, wherein the modulation of the apoptotic activity has a resultant modulation in the metalloproteinase (MMP) balance in claim 4, wherein the compound is an antibody in claim 15, wherein the antibody is a monoclonal antibody produced by commercial clone JB1a in claim 16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reason set forth in the previous Office Action mailed 12/03/08.

Applicants submit that amended Claim 1, in identifying the epitope to which the modulator compounds must bind, provides a clear teaching, which would be understood by one skilled in the art, as how to use the claimed subject matter. Applicants submit that in defining the epitope to which the beta 1 modulator compounds must bind to mediate the desired modulatory effect, the Applicants provided sufficient structural information to enable one skilled in the art to make and use the compound, as claimed.

However, the claims fail to meet the enablement requirement for the "how to make and use" prongs of the U.S.C 112, 1st paragraph. The instant fact pattern fails to indicate that a representative number of structurally related compounds is disclosed. The artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claim and consequently would not have known how to make them. Again, in order to satisfy 112, first paragraph, the specification has to teach how to make and use the polypeptides of the invention not how to identify the invention. the Examiner's position is that a compounds which bind to the beta 1 integrin in a region of amino acid residues 82-87 and functional modulation of beta 1 integrin claimed without any disclosure of any compound, does not meet the enablement requirement set forth in 35 U.S.C. §112. To satisfy this requirement, the patent application must provide adequate teaching of how to make and use the full scope of the compounds claimed, and also at least the structure or physical or chemical characteristics of a representative number of said compounds. Such requirements are not met by the disclosure describing only a receptor and screening method.

The functional activities of the claimed "compound" in claims 1 and 4 are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct *agonists* or *antagonists* to accomplish these mutually exclusive endpoints. The terms "modulates" and "alteration" indicates both inhibiting and stimulating. The skilled artisan would not have a reasonable expectation that the same compound that would *inhibit* the function of beta 1 integrin, MMP balance and apoptosis, would also serve to *enhance* the function of beta 1 integrin, MMP balance and apoptosis. Consequently the skilled artisan would not know how to use the instant invention as broadly claimed. Further, there is insufficient biochemical or structural information to enable the skilled artisan to make and use the "compound", as broadly claimed. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). The specification fails to demonstrate the effect of the claimed compounds on tissue repair. Moreover, the skilled in the art would not know what activity applicant is claiming. The claim does not contemplate a specific activity.

Applicants submit that the assertion in the rejection on page 6 of the Office Action that the "specification fails to demonstrate the effect of the claimed compounds on tissue repair" is in error. The Applicants draw the attention of the Examiner to the examples and, in particular, to the results shown in Figures 28 and 29, as described on page 45 of the instant specification which show improved histology and accordingly associated tissue repair in cells obtained from an in-

vivo mouse model. A number of the other examples, in particular the results shown in Figures 17 to 27 provide further identification of improve tissue function, following treatment with the JB1 a antibody.

However, the Examiner enabled the specification for a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a.

Applicants submit that the examples provide a clear basis for one skilled in the art to extrapolate the methodology exemplified in this specification to other disease conditions where degradation of the extracellular matrix occurs. Further, this specification makes it clear that such a therapeutic approach would be highly desirable to one skilled in the art, based on the fact that the typical, therapleutic intervention for such diseases related to the administration of anti-inflammatory, agents. As identified by the Applicants in the specification, such anti-inflammatory agents would not function to regain to regain tissue function.

However, in order for this therapy to be predictable, β1 integrin modulation must play a role in all tissue repairs. However, Grose et al (IDS reference AR) in Development 129:2303-2315 (2002) teach that their results reveal a strongly impaired migratory capacity of β1-deficient Keratinocytes in vitro and a dramatic delay in epithelial migration during wound repair in K5β1-null mice. Grose et al present the first in vivo evidence in support of findings from in vitro studies that have shown β1 integrins to be key players in cell migration. However, their results also demonstrate that keratinocytes are not totally dependent on this integrin subunit to heal their wounds. Rather, other integrins appear to compensate at least partially for the lack of β1, leading to complete, although imperfect, re-epithelialisation (page 2314, last ¶). Grose et al teach that keratinocytes proliferation rate in the β1 null keratinocytes was not reduced in early wounds and even increased in late wounds (abstract). Importantly, Grose et al teach that β1-deficient epidermis did cover the wound bed, but the epithelial architecture was abnormal. Zweers et al in J. Invest. Dermatol. 127:467-479, 2007, teaches that integrin α2β1 is required for regulation of murine wound angiogenesis but is dispensable for reepithelialization. Zweers et al teach that reepithelialization of excisional wounds of α2β1-null mice was not impaired, indicating that keratinocytes do not require adhesion to or migration on collagen for wound closure (see abstract). Applicant has no working examples demonstrating an *in vivo* treatment regiment with anti-β1 antibodies to promote any tissue repair, and the state of the art taught the "β1-deficient animals", α2β1 integrin, is dispensable for reepithelialization. Further, the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed method for promoting tissue repair using anti-β1 antibodies with a reasonable expectation of success. One skill in the art would concluded that a strategy of administering ant-β1 antibody in dermal tissue would require further understanding of the role of anti-β1 in re-epithelializtion.

11. The following new ground of rejections are necessitated by the amendment submitted 6/3/09.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 4, 15-16 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark RA. (J Invest Dermatol. 1990 Jun;94(6 Suppl):128S-134S) in view of Chantal Binda (Master Thesis. 1999. page 1-127).

Clark article teaches that during cutaneous tissue organization, numerous critical interactions occur between cells and the extracellular matrix (ECM). Cell-matrix interactions depend on the presence of ECM receptors. Many ECM receptors, known as integrins, are heterodimeric glycoproteins consisting of one α and one β chain. Integrins containing $\beta 1$ or $\beta 3$ chains are ECM receptors, whereas those containing $\beta 2$ chains are leukocyte cell-cell receptors. Clark article used porcine cutaneous wounds as a paradigm for tissue organization and probed healing wounds and adjacent normal skin with polyclonal antibodies to fibronectin and fibronectin ($\alpha 5\beta 1$) receptor. During re-epithelialization, the epidermis transits over a provisional matrix containing fibronectin. Migrating epidermal cells expressed fibronectin receptors in a bright linear peripheral pattern. At 10 days, when reepithelialization was complete and the basement membrane was re-established, the fibronectin matrix was markedly reduced and fibronectin-receptor expression was limited to the basolateral aspect of basal cells, as observed in normal epidermis. Beneath the migrating epidermis in 5-d wounds, granulation tissue had filled 80% of the wound space. Day-5 wound fibroblasts did not express fibronectin nor other $\beta 1$ integrin receptors, were randomly oriented, and contained no actin bundles. Fibronectin fibrils were assembled on the surfaces of day-5 wound fibroblasts but formed few linkages between cells. Day-7 wound fibroblasts expressed fibronectin receptors, contained peripheral cytoplasmic actin bundles consistent with a contractile fibroblast phenotype, and were coaligned across the wound in parallel array with interconnecting fibronectin fibrils. The wounds contracted between 7 and 10 days. Thus the migrating epidermis consistently expressed fibronectin receptors. Fibronectin receptors were expressed by fibroblasts just prior to wound contraction (see abstract). Clark reference concludes that fibronectin and fibronectin receptors are observed to occur in concert

during epidermal migration over a wounded surface and may perhaps facilitate this migration (see page 133S, 1st col., top ¶).

While the prior art teachings may be silent as to the compound "alteration in MMP balance", "inhibition of the apoptosis pathway", "increase in anabolism of the extracellular matrix", "wherein the modulation of the apoptotic activity has a resultant modulation in the MMP balance", causes shedding of beta 1 integrin", "results in at least one of (i) increase in inactive MMP9, and (ii) a decrease in MMP1", "may further include an increase in TIMP1" per se; the method, the product used in the reference method are the same as the claimed method. Therefore, these claimed limitations are considered inherent properties of the referenced compounds.

The Clark reference teachings differ from the claimed invention only in the recitation of a compound that binds to the β1 integrin molecule in a region of amino acid residues 82-87 comprising residues TAEKLK (SEQ ID NO:1) in claim 1, wherein the compound is an antibody in claim 15 such as JB1a in claim 16, wherein the antibody is a humanized antibody, chimeric antibody or human antibody in claim 20, or an antibody fragment of JB1a antibody in claim 21.

However, Binda in her Master thesis teaches that one inhibitory antibody called JB1A inhibits adhesion of β1 integrin to fibronectin, which is an ECM protein. JB1A antibody recgnized a continous epitope of the β1 chain spanding from amino acid residue 82-87. The amino acid sequence of this epitope is TAEKLK (claimed SEQ ID NO:1) (see page 43, 1st ¶). Binda teaches that it is feasible to develop novel monoclonal antibodies against conserved regions of the β1 integrin (see page 43, 1st ¶). Binda teaches that antibody molecules can be separated in different fragments (see page 13, last ¶ and Fig. 1). Binda teaches humanization of mouse monoclonal antibodies (see page 22) and chimeric antibodies (see page 35, 2nd ¶ in particular).

Those of skill in the art would have had reason to use the anti-β1 antibody, JB1a of the Binda master thesis as a substitute for the treatment taught in Clark article because, like the compounds taught in Clark article, anti-β1 antibody, JB1A, inhibit fibronectin receptor binding to it ligand, fibronectin. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

"[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." KSR Int'l v. Teleflex Inc., 550 U.S. 398, 416 (2007).

It would have been obvious to substitute the anti-β1 antibodies or anti-fibronectin antibodies taught by Clark for the compounds such as JB1a taught by Binda that inhibit β1 because blocking β1 inhibits binding to its ligand, fibronectin, as does blocking either anti-β1 antibodies or anti-fibronectin antibodies taught by Clark.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 1, 4, 15-16 and 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hérard et al. (Am. J. Physiol. 1996 Nov;271(5 Pt 1):L726-33.) in view of Chantal Binda (Master Thesis. 1999. page 1-127).

Hérard et al teach that fibronectin and its α5β1-integrin receptor are involved in the wound-repair process of airway epithelium. The cell migration that occurs during wound repair is dependent on modifications of the cell-matrix interaction in which extracellular matrix proteins and their receptors, the integrins, are involved. Herard et al carried out a series of wound-repair blocking experiments with the use of anti-integrin or anti-fibronectin antibodies diluted in the culture medium. We observed that fibronectin and the α5- integrin subunit were exclusively expressed by the migratory cells in the wounded area. The blocking experiments showed a significant decrease in the wound-repair index in the presence of either the anti-β1 or the anti-fibronectin antibodies. Furthermore, the addition of fibronectin to the culture medium induced a significant increase in the wound repair index. These results suggest that fibronectin and the corresponding α5β1-integrin play an important role in the process of airway epithelium wound repair (see Abstract in particular). Hérard et al teach that during wound repair, airway epithelial cells specifically express fibronectin and one of its cellular receptors, the α5β1-integrin. Fibronectin appears as a provisional matrix coordinately with the fibronectin-receptor expression on migrating airway cells and appears to be actively involved in the wound-repair process of the airway epithelium. The knowledge of the molecular components and the way in which these components work together as a dynamic system to induce airway wound repair will help to develop pharmacological strategies to accelerate or stimulate airway wound repair. Pathophysiological situations such as chronic bronchitis (the most common chronic obstructive pulmonary illnesses) will be further analyzed (see page L732 bridging ¶).

Claim 26 is included because Emphysema is COPD.

While the prior art teachings may be silent as to the compound "alteration in MMP balance", "inhibition of the apoptosis pathway", "increase in anabolism of the extracellular matrix", "wherein the modulation of the apoptotic activity has a resultant modulation in the MMP balance", causes shedding of beta 1 integrin", "results in at least one of (i) increase in inactive MMP9, and (ii) a decrease in MMP1", "may further include an increase in TIMP1" per se; the method, the product used in the reference method are the same as the claimed method. Therefore, these claimed limitations are considered inherent properties of the referenced compounds.

The Hérard et al reference teachings differ from the claimed invention only in the recitation of a compound that binds to the β1 integrin molecule in a region of amino acid residues 82-87 comprising residues TAEKLK (SEQ ID NO:1) in claim 1, wherein the compound is an antibody in claim 15 such as JB1a in claim 16, wherein the antibody is a humanized antibody, chimeric antibody or human antibody in claim 20, or an antibody fragment of JB1a antibody in claim 21.

However, Binda in her Master thesis teaches that one inhibitory antibody called JB1A inhibits adhesion of β1 integrin to fibronectin, which is an ECM protein. JB1A antibody recgnized a continous epitope of the β1 chain spanding from amino acid residue 82-87. The amino acid sequence of this epitope is TAEKLK (claimed SEQ ID NO:1) (see page 43, 1st ¶). Binda teaches that it is feasible to develop novel monoclonal antibodies against conserved regions of the β1 integrin (see page 43, 1st ¶). Binda teaches that antibody molecules can be separated in different fragments (see page 13, last ¶ and Fig. 1). Binda teaches humanization of mouse monoclonal antibodies (see page 22) and chimeric antibodies (see page 35, 2nd ¶ in particular).

Those of skill in the art would have had reason to use the anti-β1 antibody, JB1a of the Binda master thesis as a substitute for the treatment taught in Hérard et al reference because, like the compounds taught in Hérard et al reference, anti-β1 antibody, JB1A, inhibit fibronectin receptor binding to it ligand, fibronectin. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

"[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." KSR Int'l v. Teleflex Inc., 550 U.S. 398, 416 (2007).

It would have been obvious to substitute the anti-β1 antibodies or anti-fibronectin antibodies taught by Hérard et al for the compounds such as JB1a taught by Binda that inhibit β1 because blocking β1 inhibits binding to its ligand, fibronectin, as does blocking either anti-β1 antibodies or anti-fibronectin antibodies taught by Hérard et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

July 22, 2009

/Maher M. Haddad/
Maher M. Haddad, Ph.D.
Primary Examiner
Technology Center 1600